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ATTORNEY'S DOCKET NUMBER: 4-30028/A/PCT

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (if known, see 37 CFR 1.5): 09/125329

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP 98/03427	8 June 1998 (08.06.98)	10 June 1997 (10.06.97)

TITLE OF INVENTION
CRYSTAL MODIFICATION OF A PHARMACEUTICAL AGENT

APPLICANT(S) FOR DO/EO/US
ROBERT PORTMANN, URS CHRISTOPH HOFMEIER, ANDREAS BURKHARD, WALTER SCHERRER AND MARTIN SZELAGIEWICZ

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau. (See Form PCT/IB/308)
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C.371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An unexecuted Declaration and Power of Attorney (original or copy) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included.

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☐ Other items or information:

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U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
	PCT/EP 98/03427	4-30028/A/PCT

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)):

	CALCULATIONS PTO USE ONLY
Search Report has been prepared by the EPO or JPO $930	
International preliminary examination fee paid to USPTO (37 CFR 1.482) $720	
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)). $790	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO. $1,070	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4). $98	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 930
Surcharge of **$130** for furnishing the oath of declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE		
Total claims	25	- 20 =	0	X	$ 82	$ 110
Independent claims	3	- 3 =	0	X	$ 82	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+	$ 270	$
			TOTAL OF ABOVE CALCULATIONS =			$ 1040
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).						$
			SUBTOTAL =			$ 1040
Processing fee of **$130** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).					+	$
			TOTAL NATIONAL FEE =			$ 1040
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40** per property					+	$ 0
			TOTAL FEES ENCLOSED =			$ 1040
					Amount to be: refunded	$
					charged	$

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge Deposit Account No. 19-0134 in the amount of $1040 to cover the above fees. A duplicate copy of this form is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0134.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to the address associated with Customer No. 001095, which is currently:

Michael W. Glynn
Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027

Joseph J. Borovian
Agent for Applicants
Reg. No. 26,631
(908) 522-6921

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF

PORTMANN ET AL.

INTERNATIONAL APPLICATION NO: PCT/EP 98/03427

FILED: 8 JUNE 1998

U.S. APPLICATION NO: Not Yet Known

35 USC §371 DATE: Herewith

FOR: CRYSTAL MODIFICATION OF A PHARMACEUTICAL AGENT

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to calculation of the national filing fees, please amend the application as follows:

IN THE CLAIMS

Claim 3, line 1; delete "or 2".

Claim 5, line 1; replace "any one of Claims 1-4" by -- Claim 1 --.

Claim 6, line 1; replace "any one of Claims 1-5" by -- Claim 1 --.

Claim 7, lines 2 and 3; replace "any one of Claims 1-6" by -- Claim 1 --.

Claim 8, line 2; delete "according to any one of Claims 1-6,".

Claim 9; delete "or A' " and replace "any one of Claims 1-8" by -- Claim 1 --.

Claims 10, 11 and 12, line 1 of each; delete "or A' ".

Claims 10, 11 and 12, line 2 of each; replace "any one of Claims 1-9" by -- Claim 1 --.

Claim 15, line 1; replace "claim 13 or 14" by -- Claim 13 --.

Please add the following claims:

-- 16. Modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to Claim 2 but has defects in the crystal lattice. --

-- 17. Modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to Claim 3 but has defects in the crystal lattice. --

-- 18. Modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to Claim 4 but has defects in the crystal lattice. --

-- 19. Modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to Claim 5 but has defects in the crystal lattice. --

-- 20. Modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to Claim 6 but has defects in the crystal lattice. --

-- 21. Modification A' according to Claim 7 in essentially pure form. --

-- 22. Pharmaceutical preparations comprising the modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to Claim 7 and pharmaceutically usable excipients and additives. --

-- 23. Use of the modification A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to Claim 7 as a pharmaceutical preparation. --

-- 24. Use of the modification A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to Claim 7 for the preparation of pharmaceutical preparations for the treatment of epilepsy and subindications thereof. --

-- 25. A pharmaceutical preparation comprising a modification according to Claim 14 and pharmaceutically usable excipients and additives. --

REMARKS

Claims 3, 5-8 and 15 have been amended to remove their multiple dependencies.

Claims 9-12 have been amended to delete their alternative embodiments and to remove their multiple dependencies.

New Claims 16-25 have been added. In this connection,Claims 16-20 are directed to the embodiments excised from Claim 7, whereas Claims 21-25 are directed to the embodiments excised from Claims 9-12 and 15.

Respectfully submitted,

Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6921

Joseph J. Borovian
Agent for Applicants
Reg. No. 26,631

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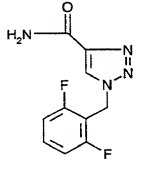
CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC

Background of the invention

The compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide of the formula



is described in the European Patent Application with the Publication No. 0 199 262 A2 (EP 199262), for example in Example 4. Valuable pharmacological properties are attributed to this compound; thus, it can be used, for example, as an antiepileptic. The compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide is obtained according to EP 199262, starting from 2,6-difluorobenzyl azide via the formation of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid, the procedure being analogous to Example 2.

EP 199262 provides no information at all about possible crystal modifications obtained. If the method according to the Example 4 is used in conjunction with Example 2, the crude 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide product obtained is finally crystallized from ethanol. However, EP 199262 gives no indication that such recrystallization is specifically to be applied, or on particular conditions that might be adopted. It has now surprisingly been found that the different crystal modifications (polymorphism) characterized below can be prepared by choice of specially selected process conditions, for example through the choice of an appropriate solvent for the recrystallization or the duration of the recrystallization.

Description of the invention

1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide can be obtained in the novel crystal modifications A, A', B and C. These crystal modifications differ with respect to their thermodynamic stability, in their physical parameters, such as the absorption pattern of IR and Raman spectra, in X-ray structure investigations and in their preparation processes.

The invention relates to the novel crystal modifications A and A', their preparation and use in pharmaceutical preparations comprising this crystal modification.

The modification A', compared with A, has defects in the crystal lattice. These are detectable, for example, by X-ray analysis, e.g. by smaller line spacings with otherwise predominantly identical lines or bands.

The novel crystal modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide melts at 242 °C (239-245 °C).

In the FT infrared (FT-IR) spectrum (KBr pellet - transmission method), modification A or A' differs from modifications B and C predominantly in the shape and in the relative intensity of many bands. Particularly characteristic are the bands at 3412 cm^{-1} and 3092 cm^{-1} [cf. Figure 1], which are not present in the FT-IR spectra of the modifications B and C. In the range 4000-600 cm^{-1}, inter alia the following bands are obtained for modification A: 3412, 3189, 3092, 1634, 1560, 1473, 1397, 1325, 1300, 1284, 1235, 1125, 1053, 1036, 1014, 885, 840, 799, 781, 723, 688 and 640 cm^{-1}. For example, the apparatus IFS 88 (Bruker) can be used for the recording of each of the FT-IR spectra.

In the FT Raman spectrum (powder - reflection method 180°), the modification A or A' differs from modifications B and C predominantly in the shape and in the relative intensity of many bands. Particularly characteristic are the band at 1080 cm^{-1} [cf. Figure 2], which is not

present in the Raman spectra of the modifications B and C. In the range 3400-300 cm^{-1}, inter alia the following bands are obtained for the modification A: 3093, 2972, 1628, 1614, 1558, 1465, 1446, 1393, 1279, 1245, 1147, 1080, 1061, 1036, 1014, 840, 724, 691, 667, 550, 499, 437 and 368 cm^{-1}. For example, the apparatus RFS 100 (Bruker) can be used for the recording of each of the FT Raman spectra.

The novel modification A has an X-ray powder pattern with characteristic lines with interplanar spacings (d values) of 10.5 Å, 5.14 Å, 4.84 Å, 4.55 Å, 4.34 Å, 4.07 Å, 3.51 Å, 3.48 Å, 3.25 Å, 3.19 Å, 3.15 Å, 3.07 Å, 2.81 Å [cf. Table 1]. The measurement can be carried out, for example, in transmission geometry on an FR 552 Guinier camera from Enraf-Nonius, Delft (The Netherlands), using copper $K\alpha_1$ radiation (wavelength λ = 1.54060 Å). The patterns recorded on X-ray film were measured using an LS-18 line scanner from Johannsson, Täby (Sweden) and evaluated using the Scanpi software (P.E.Werner, University of Stockholm).

Characteristic for the novel modification A is the thermogram in differential scanning calorimetry. It has an endothermic peak in the range from 230 °C to 260 °C. The peak temperature is 239-245 °C, and the endothermic signal is 209 J/g +/- 10 J/g. The measurement was carried out on a Perkin Elmer DSC 7 in a closed pan with a heating rate of 20 K/minute. The typical sample quantity is about 4 mg. As a typical distinguishing feature compared with the modifications B and C, the thermogram of the modification A has no further thermal signal.

Crystals fo the modification A' have the same crystal structure as modification A. They differ from the modification A in the X-ray powder pattern in that they have slightly smaller line spacings between specific pairs of lines. These are the pairs of lines with the following interplanar spacings: 3.68 Å and 3.64 Å, 3.51 Å and 3.48 Å, 3.19 Å and 3.15 Å.

In the FT-IR spectrum (KBr pellet - transmission method), the modification B differs from the

modification A or A' and C predominantly in the shape and in the relative intensity of many bands. Particularly characteristic is a band at 1678 cm^{-1} [cf. Figure 1], which is not to be observed in the corresponding spectra of the modifications A and C. In the range 4000-600 cm^{-1}, inter alia the following bands are obtained for the modification B: 3404, 3199, 3125, 1678, 1635, 1560, 1475, 1393, 1357, 1322, 1286, 1237, 1051, 1036, 1028, 889, 837, 800, 719, 667 and 645 cm^{-1}. For example, the apparatus IFS 85 (Bruker) can be used for recording of each of the FT-IR spectra.

In the FT Raman spectrum (powder - reflection method 180°), the modification B differs from the modifications A or A' and C predominantly in the shape and in the relative intensity of many bands. Particularly characteristic are the bands at 3166 cm^{-1} and 1086 cm^{-1} [cf. Figure 2], which are not present in the Raman spectra of the modifications A and C. In the range 3400-300 cm^{-1}, inter alia the following bands are obtained for the modification B: 3166, 3089, 2970, 1678, 1628, 1614, 1559, 1464, 1441, 1391, 1275, 1244, 1147, 1086, 1062, 1036, 1014, 839, 773, 724, 690, 668, 595, 549, 500, 493, 430 and 365 cm^{-1}. For example, the apparatus RFS 100 (Bruker) can be used for recording of each of the FT Raman spectra.

The modification B has an X-ray powder pattern with characteristic lines with interplanar spacings (d values) of 11.0 Å, 8.3 Å, 5.18 Å, 4.88 Å, 4.80 Å, 4.42 Å, 4.33 Å, 4.19 Å, 4.12 Å, 3.81 Å, 3.50 Å, 3.41 Å, 3.36 Å, 3.32 Å, 3.28 Å, 3.24 Å, 3.05 Å, 2.83 Å [cf. Table 1].

In the thermogram in differential scanning calorimetry, the modification B has, in addition to an endothermic signal in the range from 230 °C to 260 °C (peak temperature 239-245 °C), a weak thermal signal at 205 °C (180° - 220°C) as a typical distinguishing feature compared with the modifications A or A' and C.

In the FT-IR spectrum (KBr pellet - transmission method), the modification C differs from the modifications A or A' and B predominantly in the shape and in the relative intensity of many

bands. Particularly characteristic is a band at 3137 cm^{-1} [cf. Figure 1], which is not to be observed in the corresponding spectra of the modifications A and B.

In the range 4000-600 cm^{-1}, inter alia the following bands are obtained for the modification C: 3396, 3287, 3137, 1657, 1631, 1602, 1559, 1475, 1392, 1323, 1287, 1237, 1122, 1104, 1047, 1035, 1012, 876, 839, 797, 773, 729 and 653 cm^{-1}. For example, the apparatus IFS 85 (Bruker) can be used for recording of each of the FT-IR spectra.

In the FT Raman spectrum (powder - reflection method 180°), the modification C differs from the modifications A or A' and B predominantly in the shape and in the relative intensity of many bands. Particularly characteristic are the bands at 3137 cm^{-1} and 1602 cm^{-1} [cf. Figure 2], which are not present in the Raman spectra of the modifications A and B. In the range 3400-300 cm^{-1}, inter alia the following bands are obtained for the modification C: 3137, 3080, 3012, 2971, 1673, 1629, 1602, 1561, 1436, 1271, 1248, 1105, 1065, 1035, 1013, 839, 800, 767, 726, 690, 672, 593, 549, 500, 492, 435 and 370 cm^{-1}. For example, the apparatus RFS 100 (Bruker) can be used for recording of each of the FT Raman spectra.

The modification C has an X-ray powder pattern with characteristic lines with interplanar spacings (d values) of 9.0 Å, 4.73 Å, 4.65 Å, 3.75 Å, 3.54 Å, 3.42 Å, 3.25 Å [cf. Table 1]. In the thermogram in differential scanning calorimetry, the modification C has, in addition to an endothermic signal in the range of 230 °C to 260 °C (peak temperature 239-245 °C), a very broad, weak, exothermic signal in the region of 180 °C compared with the modifications A or A' and B.

Table 1: Characterization of the modifications A, B and C (X-ray powder patterns):

Modification A:		Modification B:		Modification C:	
d [Å]	Intensity	d [Å]	Intensity	d [Å]	Intensity
10.9	weak	11.0	medium	9.0	medium
10.5	medium	8.3	medium	7.0	weak
6.6	weak	8.1	very weak	5.49	weak
5.63	weak	5.68	very weak	5.11	very weak
5.25	weak	5.18	very strong	4.80	weak
5.14	medium	5.11	weak	4.73	strong
4.94	weak	4.88	medium	4.65	very strong
4.84	very strong	4.80	strong	4.47	very weak
4.55	strong	4.71	very weak	4.19	very weak
4.42	very weak	4.61	weak	4.11	very weak
4.34	medium	4.45	weak	3.98	very weak
4.23	very weak	4.42	strong	3.83	very weak
4.16	weak	4.33	very strong	3.75	strong
4.07	medium	4.19	medium	3.73	weak
4.01	weak	4.12	strong	3.54	medium
3.68	very weak	4.09	weak	3.50	weak
3.64	very weak	3.99	very weak	3.42	strong
3.60	weak	3.95	very weak	3.25	medium
3.56	weak	3.84	weak	2.88	very weak
3.51	medium	3.81	medium	2.80	very weak
3.48	medium	3.65	weak	2.74	very weak
3.38	very weak	3.61	very weak	2.67	very weak
3.25	strong	3.58	very weak	2.64	weak
3.19	medium	3.54	weak		
3.15	medium	3.50	medium		
3.11	weak	3.47	very weak		
3.07	medium	3.41	medium		
2.93	very weak	3.36	very strong		
2.87	very weak	3.32	strong		
2.81	medium	3.28	medium		
2.76	weak	3.24	medium		
2.73	very weak	3.10	weak		
2.68	weak	3.07	weak		
2.62	very weak	3.05	medium		
2.53	weak	2.93	weak		
2.43	weak	2.88	weak		
2.40	very weak	2.87	very weak		
		2.83	medium		
		2.66	weak		
		2.63	very weak		
		2.55	weak		
		2.50	weak		

		2.46	weak		
		2.44	weak		
		2.37	weak		
		2.35	weak		

Single crystal X-ray analysis:

Crystal quality and unit cell of modifications A, B, and C were verified by Weissenberg and precession photographs. The intensities were measured on a four-axis Nonius CAD-4 diffractometer. The structures were solved with the SHELXS-97 and refined with the SHELXL-97 software.

Modification A

Space group: $Pna2_1$ - orthorhombic

Cell dimensions:

a = 24.756 (5)Å	b = 23.069 (4)Å	c = 5.386 (1)Å
V = 3075.9 Å^3	Z = 12	D_x = 1.543 gcm^{-3}
V per formula:	V_z = 256.3 Å^3	

9011 unique reflections; 2479 thereof significant with $I > 2\sigma(I)$. 557 parameters refined. Position of all H atoms found by difference Fourier maps and refined isotropically. Reliability index R_1: 3.65% (wR_2 for all 9011 reflections: 11.34%).

Modification B

Space group: P $\bar{1}$ -triclinic

Cell dimensions:

a = 5.326(1) Å	b = 11.976(2) Å	c = 17.355(3) Å
α = 107.22(3)°	β = 92.17(3)°	γ = 102.11(3)°
V = 1027.9 Å^3	Z = 4	D_x = 1.539 gcm^{-3}
V per formula	V_z = 257.0 Å^3	

4934 unique reflections; 834 thereof significant with $I > 2\sigma(I)$. 232 parameters refined. Position of all H atoms found by difference Fourier maps and refined isotropically. Reliability index R_1: 4.20% (wR_2 for all 4934 reflections: 7.93%).

Modification C

Space group: $P2_1/C$ - monoclinic

Cell dimensions:

a = 10.982(2) Å	b = 5.350(1) Å	c = 17.945(3) Å
	β = 91.59(1)°	
V = 1053.9 Å^3	Z = 4	D_x = 1.501 gcm^{-3}
V per formula:	V_z = 263.5 Å^3	

3073 unique reflections; 1071 thereof significant with $I > 2\sigma(I)$. 187 parameters refined. Position of all H atoms found by difference Fourier maps and refined isotropically. Reliability index R_1: 5,02% (wR_2 for all 3073 reflections: 14.55%).

Modifications A, A', B and C have valuable pharmacological properties; in particular, they can be used for the treatment of epilepsy.

The modification A or A' has significant advantages compared with the modification B and compared with the modification C. Thus, for example, comprehensive thermodynamic investigations, such as thermomicroscopy, X-ray powder diffractometry, DSC, solubility tests and other experiments, have shown that the modification A or A' surprisingly has substantially better thermodynamic stability than the modifications B and C. Modification C, which can be obtained only under specific conditions, is the least stable of the three modifications. The crystals of the modification C are converted into modification B at as low as room temperature within a few weeks. The modification C is converted either into the modification A or A' or into the modification B, depending on experimental conditions.

It is particularly important for drug that its pharmaceutical formulation ensures high and reproducible stability over a long period. These preconditions are fulfilled by incorporation of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide of the crystal modification A or A', owing to its high thermodynamic stability. In particular, this is displayed in a solid pharmaceutical dosage form.

A constant stability also permits reproducible bioavailability of an active ingredient. If an active ingredient is subjected to a conversion process, this may readily also cause the bioavailability to fluctuate, which is undesirable. Accordingly, pharmaceutical active ingredients or polymorphic forms thereof which are of primary interest for pharmaceutical developments are those which exhibit high stability and do not have the above-mentioned disadvantages. The crystal modification A or A' fulfils these preconditions.

Furthermore, the modification A or A' has, for example, a slower dissolution rate in water or in gastric fluid (so-called "slow-release effect"). This effect can be utilized primarily for long-term therapy where a slow or delayed release is desired.

The invention relates to the modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized by the following absorptions in the infrared spectrum (KBr pellet - transmission method): bands at 3092 cm^{-1} and 3412 cm^{-1}.

The invention relates to the modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized by characteristic lines with interplanar spacings (d values) of 10.5 Å, 5.14 Å, 4.84 Å, 4.55 Å, 4.34 Å, 4.07 Å, 3.51 Å, 3.48 Å, 3.25 Å, 3.19 Å, 3.15 Å, 3.07 Å and 2.81 Å, determined by means of an X-ray powder pattern.

The invention relates to the modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized by the characteristic lines with interplanar spacings (d values)

as shown in Table 1.

The invention relates to the modification A of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized by an endothermic peak in the range from 230 °C to 260 °C, the peak temperature being 239-245 °C and the endothermic signal being 209 J/g +/- 10 J/g.

Furthermore, the invention relates to the crystal modification A' which, compared with modification A, has defects in the crystal lattice.

The invention relates to the modification A' which, compared with modification A, has smaller line spacings between the pairs of lines with interplanar spacings 3.68 Å and 3.64 Å, 3.51 Å and 3.48 Å, and 3.19 Å and 3.15 Å.

The invention relates to the essentially pure form of the modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide. The term "essentially pure form" means purity of >95%, in particular >98%, primarily >99%, based on the modification A or A'.

The invention relates to pharmaceutical preparations comprising the modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide. The invention relates in particular to corresponding pharmaceutical preparations for the treatment of epilepsy and subindications thereof. The invention relates to the use of the modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide for the preparation of pharmaceutical preparations, in particular for the treatment of epilepsy and subindications thereof.

The novel modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide can be used, for example, in the form of pharmaceutical preparations which comprise a therapeutically effective amount of the active ingredient, if desired together with inorganic or organic, solid or liquid, pharmaceutically usable carriers, which are suitable for enteral, for

example oral, or parenteral administration. Furthermore, the novel modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide can be used in the form of preparations which can be administered parenterally or of infusion solutions. The pharmaceutical preparations may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical preparations comprise from about 0.1% to 100%, in particular from about 1% to about 50%, of lyophilisates to about 100% of the active ingredient.

The invention also relates to the use of modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide as a drug, preferably in the form of pharmaceutical preparations. The dosage may depend on various factors, such as method of administration, species, age and/or individual condition. The doses to be administered daily are between about 0.25 and about 10 mg/kg in the case of oral administration, and preferably between about 20 mg and about 500 mg for warm-blooded species having a body weight of about 70 kg.

The preparation of modification A or A' is carried out, for example, as described in the embodiments below.

Preparation of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide

Example 1:

A suspension of methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate (about 62 parts by weight), methanol (475.2 parts by weight) and anhydrous ammonia (29.4 parts by weight) is stirred for about 24 hours at 50-55°C in a closed vessel. The suspension is cooled to about 20°C and stirred for about a further 2 hours. The product is isolated by filtration, washed with methanol (240 parts by weight) and dried at 40-60°C in vacuo. Yield: 57.2 parts by weight = 98%. Modification A.

The starting compounds can be prepared, for example, as follows:

A mixture of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid (167.1 parts by weight), methanol (552 parts by weight) and 96% sulfuric acid (35.7 parts by weight) is stirred for about 5 hours at 60-66°C. The suspension is cooled to about 20°C and stirred for about a further 2 hours. The product is isolated by filtration and washed with methanol (198 parts by weight). A yield of about 160 parts by weight is obtained by drying at 40-60°C in vacuo.

Example 2:

1 N sodium hydroxide solution (0.11 ml) is added to a mixture of 4-cyano-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole (2.20 g) and water (44 ml) at an external temperature of 95-100°C while stirring. After 90 minutes, the suspension is cooled to 10°C and the product is isolated by filtration, washed with water and dried at about 60°C in vacuo. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide is obtained in this manner; yield: 99.2% by weight. Modification A.

The starting material can be prepared, for example, as follows:

4-Cyano-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole

A mixture of 2,6-difluorobenzyl azide (34.2 g), 2-chloroacrylonitrile (17.73 g) and water (125 ml) is stirred for 24 hours at about 80°C. By increasing the external temperature to about 130°C, excess 2-chloroacrylonitrile is distilled off. The semisolid mixture is cooled to about 40°C, cyclohexane (50 ml) is added to the suspension and the mixture is brought to about 20°C and stirred for about 2 hours. The product is isolated by filtration and washed with cyclohexane (75 ml) and then with water (50 ml). The moist product is mixed with water (100 ml), the suspension is filtered and the product is washed with water (50 ml) and dried at about 60°C in vacuo. Yield: 38.04 g = 86%.

Exampies of the recrystallization of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide

Example 3:

1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide (75.0 g) is dissolved in formic acid

(360 ml) at 50-55°C by stirring. The solution is discharged in the course of 1 hour onto stirred methanol (375 ml) at about 20°C, a suspension forming. After stirring has been continued for 2 hours at about 20°C, the product is isolated by filtration, washed with methanol (750 ml) and dried at about 60°C in vacuo. Yield: 69.6 g = 92.8%. Modification A.

Example 4:

1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide (22.86 kg) is dissolved in formic acid (111.6 kg) at 58-63°C while stirring. The solution is discharged in the course of about 2 hours onto stirred methanol (131.9 l) at 20-25°C, after which washing with formic acid (7.6 kg) is carried out. A suspension forms. After stirring has been continued for at least 3 hours at about 20°C, the product is isolated by filtration and washed with methanol (187.5 l). By drying in vacuo at about 60°C, the product is obtained as modification A in a yield of 93-94%.

Example 5:

1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide (pure active ingredient; 4.0 g) is dissolved in 96% ethanol (500 ml, without denaturing agent) at about 80°C while stirring. The solution is filtered into a suction bottle (1 litre) at about 20°C (glass suction filter, pore size 10-20 µm), a suspension forming. After stirring has been continued for 5 minutes at about 20°C and for 15 minutes at about 0°C, the product is isolated by filtration (about 0° to about 20°C). The solvent-moist product (9.6 g) is investigated without subsequent drying. Modification A'.

Formulation Example 1:

Film-coated tablets each containing, for example, 100, 200 or 400 mg of modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide with the following composition per dosage unit:

Core material	mg	mg	mg

Active ingredient	100.00	200.00	400.00
Anhydrous, colloidal silica	0.88	1.75	3.5
Microcrystalline cellulose	36.62	73.25	146.50
Hydroxypropylmethyl-cellulose	5.00	10.00	20.00
Lactose	20.00	40.00	80.00
Magnesium stearate	2.00	4.00	8.00
Maize starch	10.00	20.00	40.00
Sodium carboxymethyl-cellulose	5.00	10.00	20.00
Sodium laurylsulfate	0.50	1.00	2.00
Film coat	mg	mg	mg
Hydroxypropylmethyl-cellulose	3.22	6.43	12.87
Red iron oxide	0.04	0.09	0.18
Polyethylene glycol 8000, flakes	0.58	1.16	2.32
Talc	2.33	4.66	9.31
Titanium dioxide	0.83	1.66	3.32

The active ingredient is granulated with demineralised water. Milled lactose, maize starch, Avicel PH 102, cellulose-HP-M-603 and sodium laurylsulfate are added to the above mixture and granulated with demineralised water.

The moist material is dried and milled. After the addition of the remaining ingredients, the homogeneous mixture is compressed to give tablet cores having the stated active ingredient content.

The tablet cores are coated with the film coat which is formed from the appropriate ingredients, the latter being dissolved or being suspended in water or in small amounts of ethanol with 5% of isopropanol.

Description of the Figures

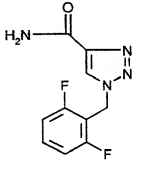
Figure 1 shows the FT-IR spectra of the KBr pellets of modifications A, B and C.

Figure 2 shows the FT-Raman spectra of the powder of modification A, B and C.

In both Figures, the modification A is denoted by the symbol *, the modification B by the symbol ** and the modification C by the symbol ***.

Patent Claims

1. Modification A of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide of the formula



characterized by characteristic lines at interplanar spacings (d values) of 10.5 Å, 5.14 Å, 4.84 Å, 4.55 Å, 4.34 Å, 4.07 Å, 3.51 Å, 3.48 Å, 3.25 Å, 3.19 Å, 3.15 Å, 3.07 Å, 2.81 Å, determined by means of an X-ray powder pattern.

2. Modification according to Claim 1, characterized by an X-ray powder pattern having the following characteristic lines at interplanar spacings (d values) of 10.9 Å (weak), 10.5 Å (medium), 6.6 Å (weak), 5.63 Å (weak), 5.25 Å (weak), 5.14 Å (medium), 4.94 Å (weak), 4.84 Å (very strong), 4.55 Å (strong), 4.42 Å (very weak), 4.34 Å (medium), 4.23 Å (very weak), 4.16 Å (weak), 4.07 Å (medium), 4.01 Å (weak), 3.68 Å (very weak), 3.64 Å (very weak), 3.60 Å (weak), 3.56 Å (weak), 3.51 Å (medium), 3.48 Å (medium), 3.38 Å (very weak), 3.25 Å (strong), 3.19 Å (medium), 3.15 Å (medium), 3.11 Å (weak), 3.07 Å (medium), 2.93 Å (very weak), 2.87 Å (very weak), 2.81 Å (medium), 2.76 Å (weak), 2.73 Å (very weak), 2.68 Å (weak), 2.62 Å (very weak), 2.53 Å (weak), 2.43 Å (weak), 2.40 Å (very weak).

3. Modification according to Claim 1 or 2, characterized by the following absorptions in the FT-IR spectrum (KBr pellet - transmission method) 3092 cm^{-1} and 3412 cm^{-1}.

4. Modification according to Claim 3, characterized by the following absorptions in the FT-IR spectrum (KBr pellet - transmission method): 3412, 3189, 3092, 1634, 1560, 1473, 1397, 1325, 1300, 1284, 1235, 1125, 1053, 1036, 1014, 885, 840, 799, 781, 723, 688 and 640 cm^{-1}.

5. Modification according to any one of Claims 1-4, characterized by the following absorptions in the FT-Raman spectrum (powder - reflection method 180°): 3093, 2972, 1628, 1614, 1558, 1465, 1446, 1393, 1279, 1245, 1147, 1080, 1061, 1036, 1014, 840, 724, 691, 667, 550, 499, 437 and 368 cm^{-1}.

6. Modification A according to any one of Claims 1-5, characterized by an endothermic peak in the range from 230 °C to 260 °C, the peak temperature being 239-245 °C and the endothermic signal being 209 J/g +/- 10 J/g.

7. Modification A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, characterized in that it is identical to the modification A according to any one of Claims 1-6 but has defects in the crystal lattice.

8. Modification A' according to Claim 7, characterized by line spacings, smaller compared to modification A according to any one of Claims 1-6, between the pairs of lines at interplanar spacings 3.68 Å and 3.64 Å, 3.51 Å and 3.48 Å, and 3.19 Å and 3.15 Å.

9. Modification A or A' according to any one of Claims 1-8 in essentially pure form.

10. Pharmaceutical preparations comprising the modification A or A' of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to any one of Claims 1-9 and pharmaceutically usable excipients and additives.

11. Use of the modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to any one of Claims 1-9 as a pharmaceutical preparation.

12. Use of the modification A or A' of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to any one of Claims 1-9 for the preparation of pharmaceutical preparations for the treatment of epilepsy and subindications thereof.

13. A modification of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide characterized by bands at 3412 cm^{-1} and 3092 cm^{-1} in the FT-IR spectrum.

14. A modification of the compound1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide characterized by a band at 1080 cm^{-1} in the FT-Raman spectrum.

15. A pharmaceutical preparation comprising a modification according to claim 13 or 14 and pharmaceutically usable excipients and additives.

Figure 1

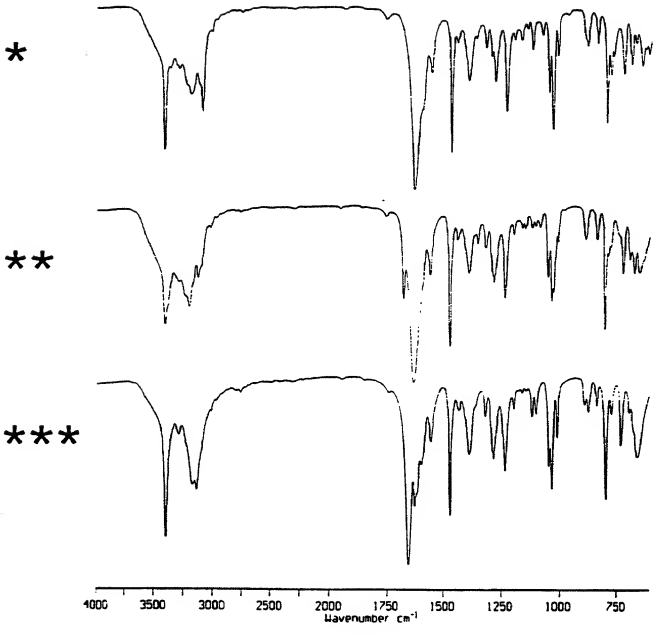
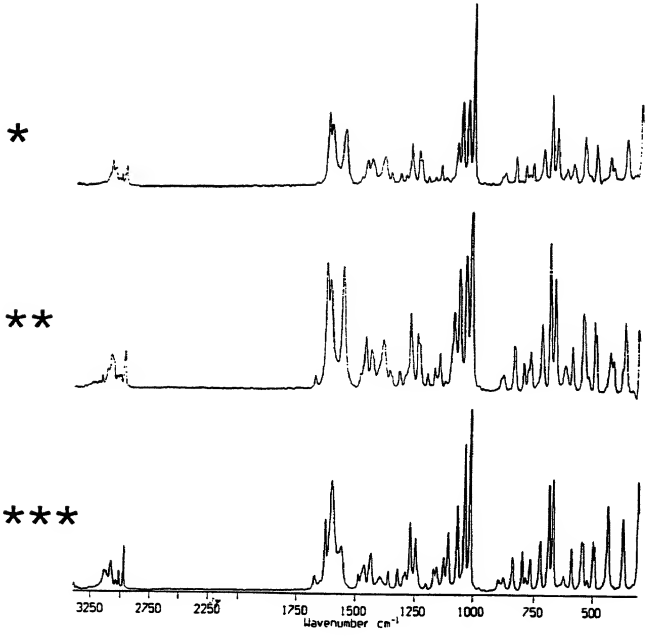

*
**
***
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
Wavenumber cm-1

Figure 2



US Case **4 -30028/A**

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

☐ Original ☐ Supplemental ☒ Substitute

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

Crystal modification of a pharmaceutical agent

the specification of which:

☐ is attached hereto.

☐ was filed on _____ (day/month/year) as Application No. _____

and, if this box (☐) contains an *

☐ was amended on _____ (day/month/year)

☒ was filed as Patent Cooperation Treaty international Application No.

PCT/EP98/03427 on **8.6.98** (day/month/year)

and, if this box (☐) contains an *

☒ entered the national stage in the United States and was accorded Application No.

09/125,329

and, if this box (☐) contains an *

☐ was amended, subsequent to entry into the national stage, on _____ (day/month/year)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above and, if this application was filed as a Patent Cooperation Treaty international application, by any amendments made during the international stage (including any made under Patent Cooperation Treaty Rule 91, Article 19 and Article 34).

I acknowledge my duty to disclose all information which is known by me to be material to the patentability of this application as defined in 37 C.F.R. § 1.56.

I hereby claim the benefit under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below and under 35 U.S.C. §365(a) of any Patent Cooperation Treaty international application(s) designating at least one country other than the United States listed below and have also listed below any foreign application(s) for patent or inventor's certificate and Patent Cooperation Treaty international application(s) designating at least one country other than the United States for the same subject matter and having a filing date before that of the application the priority of which is claimed for that subject matter:

COUNTRY/REGION (OR P.C.T.)	APPLICATION No.	FILING DATE (day/month/year)	PRIORITY CLAIMED	
Switzerland	**1404/97**	**10.06.97**	☒ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No

I hereby claim the benefit under 35 U.S.C. § 119 (e) of any United States provisional application(s) listed below:

APPLICATION NO.	FILING DATE (day/month/year)

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) listed below and under 35 U.S.C. §365(c) of any Patent Cooperation Treaty international application(s) designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner required by the first paragraph of 35 U.S.C. §112, I acknowledge my duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date(s) of the prior application(s) and the national or Patent Cooperation Treaty international filing date of this application:

United States Application No.	United States Filing Date (day/month/year)	Status (Pending, Abandoned or U.S. Patent No.)	International Application No.	and Filing Date

I hereby appoint the registered practitioners associated with Customer No. 001095, respectively and individually, as my attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

If these brackets contain an X [X], I hereby authorize the registered practitioners associated with Customer No. 001095 and any others acting on my behalf to take any action relating to this application based on communications from the Patents and Trademarks Division of Novartis Services AG, Basle, Switzerland, or an affiliate thereof or a successor thereto, without direct communication from me.

Please address all communications to Michael W. Glynn, Novartis Corporation, Patent and Trademark Department, 564 Morris Avenue, Summit, NJ 07901-1027.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Full name of sole or first joint inventor	1-00 **Robert PORTMANN**
Inventor's signature	Robert Portmann — Date 14.9.98 (day/month/year)
Residence	CHX **Pratteln, Switzerland**
Citizenship	**Swiss**
Post Office Address	**Unterer Rütschetenweg 38** **4133 Pratteln** **Switzerland**

IMPORTANT: Before this declaration is signed, the patent application (the specification, the claims and this declaration) must be read and understood by each person signing it, and no changes may be made in the application after this declaration has been signed.

Full name of second joint inventor, if any 2-00 **Urs Christoph HOFMEIER**

Inventor's signature Urs Hofmeier Date 21.9.98 (day/month/year)

Residence CH X **St. Pantaleon, Switzerland**

Citizenship **Swiss**

Post Office Address **Hauptstrasse 30**
4421 St. Pantaleon
Switzerland

Full name of third joint inventor, if any 3-00 **Andreas BURKHARD**

Inventor's signature Andreas Burkhard Date 17/9/98 (day/month/year)

Residence CH X **Basel, Switzerland**

Citizenship **Swiss**

Post Office Address **Blotzheimerstrasse 29**
4055 Basel
Switzerland

Full name of fourth joint inventor, if any 4-00 **Walter SCHERRER**

Inventor's signature Walter Scherrer Date 14.9.98 (day/month/year)

Residence CH X **Rheinfelden, Switzerland**

Citizenship **Swiss**

Post Office Address **Habsburgerstrasse 62**
4310 Rheinfelden
Switzerland

Full name of fifth joint inventor, if any 5-00 **Martin SZELAGIEWICZ**

Inventor's signature Martin Szelagiewicz Date 17. 9. 98 (day/month/year)

CHX

Residence **Münchenstein, Switzerland**

Citizenship **Swiss**

Post Office Address **Christoph-Merian-Strasse 1**
4142 Münchenstein
Switzerland

Full name of sixth joint inventor, if any

Inventor's signature _____ Date _____ (day/month/year)

Residence

Citizenship

Post Office Address

Full name of seventh joint inventor, if any

Inventor's signature _____ Date _____ (day/month/year)

Residence

Citizenship

Post Office Address